PROGRESS REVIEW ON THE COORDINATED IMPLEMENTATION OF THE NATIONAL NANOTECHNOLOGY INITIATIVE 2011 ENVIRONMENTAL, HEALTH, AND SAFETY RESEARCH STRATEGY

National Science and Technology Council
Committee on Technology

Subcommittee on Nanoscale Science,
Engineering, and Technology

June 2014

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About this Document

This document is intended to provide an overview of progress on the coordinated implementation of the 2011 NNI Environmental, Health, and Safety (EHS) Research Strategy that was developed by the NSET Subcommittee's Nanotechnology Environmental and Health Implications (NEHI) Working Group. The 2011 NNI EHS Research Strategy aims to ensure the responsible development of nanotechnology by providing guidance to the Federal agencies that produce the scientific information for risk assessment, risk management, regulatory decision making, product use, research planning, and public outreach. It describes the NNI's EHS vision and mission, the state of the science, and the research needed to achieve the vision.

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NATIONAL SCIENCE AND TECHNOLOGY COUNCIL
COMMITTEE ON TECHNOLOGY (CoT)
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National Nanotechnology Coordination Office:
Lloyd J. Whitman, Interim Director
Lisa E. Friedersdorf, Deputy Director

NSET Subcommittee Participants

Office of Science and Technology Policy (OSTP)
Altaf H. Carim*

Office of Management and Budget (OMB)
Danielle Jones*
James Kim*
Celinda Marsh*

Consumer Product Safety Commission (CPSC)†
Mary Ann Danello*
Treye A. Thomas*

Department of Commerce (DOC)

Bureau of Industry and Security (BIS)
Kelly Gardner*

Economic Development Administration (EDA)
Thomas Guevara*

National Institute of Standards and Technology (NIST)
Heather Evans*
Ajit Jillavenkatesa*
Debra L. Kaiser

U.S. Patent and Trademark Office (USPTO)
Gladys Corcoran*
David R. Gerk*
Bruce Kisliuk*

Department of Defense (DOD)
Mostafiz Chowdhury
Jeffrey DePriest*
Akbar Khan*
Heather Meeks
Brian D. Pate
Gernot S. Pomrenke*
Lewis E. Sloter*
David M. Stepp*
Peter Vandeventer

Department of Education (DOEd)
Peirce Hammond*

Department of Energy (DOE)
Harriet Kung*
George Maracas*
John C. Miller*
Andrew R. Schwartz*
Brian G. Valentine*

Department of Health and Human Services (DHHS)

Agency for Toxic Substances and Disease Registry (ATSDR)
Candis M. Hunter

Food and Drug Administration (FDA)
Jed Costanza*

National Institute for Occupational Safety and Health (NIOSH)
Charles L. Geraci*
Vladimir V. Murashov*

National Institutes of Health (NIH)
Piotr Grodzinski*
Lori Henderson*

Department of Homeland Security (DHS)
Richard T. Lareau
Ron McNeal*

Department of the Interior (DOI)

U.S. Geological Survey (USGS)
Sarah Gerould*

Department of Justice (DOJ)

National Institute of Justice (NIJ)
Joseph Heaps*

Department of Labor (DOL)

Occupational Safety and Health Administration (OSHA)
Janet Carter*

Department of State (DOS)
Christopher M. Cannizzaro*
Ken Hodgkins*

Department of Transportation (DOT)
Peter Chipman*
Jonathan R. Porter*

Department of the Treasury (DOTreas)
John F. Bobalek*

Environmental Protection Agency (EPA)
Tina Bahadori*
William Boyes*
Nora F. Savage*
Philip G. Sayre*

Intelligence Community (IC)

Office of the Director of National Intelligence (ODNI)
Richard Ridgley*

National Reconnaissance Office (NRO)
Matthew Cobert*

National Aeronautics and Space Administration (NASA)
Michael A. Meador*

National Science Foundation (NSF)
Parag R. Chitnis*
Khershed Cooper*
Fred Kronz
Thomas P. Rieker*
Mihail C. Roco*
Grace J. Wang*

Nuclear Regulatory Commission (NRC)†
Brian Thomas*

U.S. Department of Agriculture (USDA)

Agriculture Research Service (ARS)
Robert Fireovid*

Forest Service (FS)
World L.-S. Nieh*
Theodore H. Wegner*

National Institute of Food and Agriculture (NIFA)
Hongda Chen*

U.S. International Trade Commission (USITC)†
Elizabeth R. Nesbitt*

KEY * **Official NSET Representative**
† **Independent commission that is represented on NSET but is non-voting**

NATIONAL SCIENCE AND TECHNOLOGY COUNCIL
COMMITTEE ON TECHNOLOGY (CoT)
SUBCOMMITTEE ON NANOSCALE SCIENCE, ENGINEERING, AND TECHNOLOGY (NSET)
NANOTECHNOLOGY ENVIRONMENTAL AND HEALTH IMPLICATIONS (NEHI) WORKING GROUP

NEHI Working Group Co-Chairs:
John Howard, National Institute for Occupational Safety and Health
Treye Thomas,* Consumer Product Safety Commission

NEHI Executive Secretary:
Tarek R. Fadel, National Nanotechnology Coordination Office

NEHI Working Group Members

Office of Science and Technology Policy (OSTP)
Altaf H. Carim

Office of Management and Budget (OMB)
Danielle Jones
James Kim

Consumer Product Safety Commission (CPSC)†
Mary Ann Danello
Treye A. Thomas

Department of Commerce (DOC)
National Institute of Standards and Technology (NIST)
Debra L. Kaiser

Department of Defense (DOD)
T. Matthew Cho
Igor Linkov
Jeffrey Steevens
Patricia M. Underwood

Department of Energy (DOE)
Andrew Schwartz

Department of Health and Human Services (DHHS)
Agency for Toxic Substances and Disease Registry (ATSDR)
Candis M. Hunter
Food and Drug Administration (FDA)
Jed Costanza
National Institute for Occupational Safety and Health of the Centers for Disease Control and Prevention (NIOSH/CDC)
Charles L. Geraci
Vladimir V. Murashov
National Institute of Environmental Health Sciences of the National Institutes of Health (NIEHS/NIH)
Sri Nadadur
Christopher Weis
National Cancer Institute of the National Institutes of Health (NCI/NIH)
Scott McNeil
Anil Patri

Department of Labor (DOL)
Occupational Safety and Health Administration (OSHA)
Janet Carter
Rebecca Reindel

Department of State (DOS)
Christopher M. Cannizzaro

Department of the Interior (DOI)
U.S. Geological Survey (USGS)
Sarah Gerould

Environmental Protection Agency (EPA)
William Boyes
Nora F. Savage
Philip G. Sayre
Thabet Tolaymat

National Nanotechnology Coordination Office
Lisa E. Friedersdorf
Shelah Morita (AAAS Fellow)
Lloyd J. Whitman

National Science Foundation (NSF)
Mihail C. Roco
Alan J. Tessier

U.S. Department of Agriculture (USDA)
Forest Service (FS)
World Nieh
National Institute of Food and Agriculture (NIFA)
Hongda Chen

U.S. International Trade Commission (USITC)†
Elizabeth Nesbitt

KEY * NNI Coordinator for Environmental, Health, and Safety research
† Independent commission that is represented on NSET but is non-voting

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Chief Editor: Debra L. Kaiser (NIST)

Project Manager: Tarek R. Fadel (NNCO, contractor)

Writing Team Co-Chairs

- Nanomaterial Measurement Infrastructure: Debra L. Kaiser (NIST)
- Human Exposure Assessment: Cathy Fehrenbacher (EPA), Vladimir V. Murashov (NIOSH)
- Human Health: Jeffrey Steevens (DOD), Christopher Weis (NIEHS)
- Environment: Alan J. Tessier (NSF), Thabet Tolaymat (EPA)
- Risk Assessment and Risk Management Methods: Carlos Peña (FDA), Treye Thomas (CPSC)
- Informatics and Modeling: Martin Fritts (NIST), Sally Tinkle (formerly with NNCO, now with the Science and Technology Policy Institute)

Additional Writing Team Members (in alphabetical order by member's last name): William Boyes (EPA), Christopher M. Cannizzaro (DOS), Altaf H. Carim (OSTP), Janet Carter (OSHA), Matthew Cho (DOD), Jed Costanza (FDA), Heather Evans (NIST), Charles L. Geraci (NIOSH), Barbara Karn (formerly with NSF), and Mihail C. Roco (NSF)

KEY * **Affiliations as of June 2014**

EXECUTIVE OFFICE OF THE PRESIDENT
NATIONAL SCIENCE AND TECHNOLOGY COUNCIL
WASHINGTON, D.C. 20502

June 23, 2014

Dear Colleagues,

On behalf of the National Nanotechnology Initiative (NNI), I am pleased to release the *Progress Review on the Coordinated Implementation of the 2011 NNI Environmental, Health, and Safety Research Strategy*.

This document was prepared by the Nanotechnology Environmental and Health Implications (NEHI) Working Group, a subgroup of the Subcommittee on Nanoscale Science, Engineering, and Technology under the Committee on Technology of the National Science and Technology Council. Over a two-year period, the NEHI Working Group surveyed and analyzed nanotechnology environmental, health, and safety (nanoEHS) research supported by the Federal Government that addressed the needs enumerated in the research strategy. The product of this effort is an extensively annotated report documenting a wide range of research activities, accomplishments, and collaborations undertaken from 2009 through 2012.

Well-coordinated nanoEHS research is essential to ensure the responsible development and commercialization of nanotechnology, a key field contributing to American innovation, advanced manufacturing, and economic competitiveness. The *2011 NNI EHS Research Strategy* continues to guide Federal agencies generating the scientific information underpinning risk assessment, risk management, risk communication, regulatory decision making, product manufacture and use, research planning, and public outreach. Progress in this area is essential to establishing the regulatory certainty needed for companies to bring their nanotechnology products to market, and to ensuring these products are safe for use throughout their life cycle. The Committee on Technology offers this report to the NNI's stakeholders to document the extensive, ongoing coordination and cooperation among the NNI agencies, as well as the breadth and depth of their recent nanoEHS research activities in support of the responsible development of nanotechnology.

Sincerely,

Thomas Kalil
Chair, Committee on Technology and
Deputy Director for Technology and Innovation
Office of Science and Technology Policy

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Executive Summary

This document provides an overview of progress on the implementation and coordination of the 2011 NNI Environmental, Health, and Safety (EHS) Research Strategy that was developed by the Nanoscale Science, Engineering, and Technology Subcommittee's Nanotechnology Environmental and Health Implications (NEHI) Working Group. Consistent with the adaptive management process described in this strategy, the NEHI Working Group has made significant progress through the use of various evaluation tools to understand the current status of nanotechnology-related EHS (nanoEHS) research and the Federal nanoEHS research investment.

Most notably, the participating agencies reported to the NEHI Working Group examples of ongoing, completed, and anticipated EHS research (from FY 2009 through FY 2012) relevant to implementation of the 2011 NNI EHS Research Strategy. These examples, described in this document, demonstrate the breadth of activities in all six core research areas of the 2011 NNI EHS Research Strategy: Nanomaterial Measurement Infrastructure, Human Exposure Assessment, Human Health, Environment, Risk Assessment and Risk Management Methods, and Informatics and Modeling. Overall, coordination and implementation of the 2011 NNI EHS Strategy across the NEHI agencies has enabled:

- Development of comprehensive measurement tools that consider the full life cycles of engineered nanomaterials (ENMs) in various media.
- Collection of exposure assessment data and resources to inform workplace exposure control strategies for key classes of ENMs.
- Enhanced understanding of the modes of interaction between ENMs and physiological systems relevant to human biology.
- Improved assessment of transport and transformations of ENMs in various environmental media, biological systems, and over full life cycles.
- Development of principles for establishing robust risk assessment and risk management practices for ENMs and nanotechnology-enabled products that incorporate ENMs, as well as approaches for identifying, characterizing, and communicating risks to all stakeholders.
- Coordination of efforts to enhance data quality, modeling, and simulation capabilities for nanotechnology, towards building a collaborative nanoinformatics infrastructure.

Extensive collaboration and coordination among the NEHI agencies as well as with international organizations is evident by the numerous research examples and by other activities such as co-sponsored workshops and interagency agreements described in this review document. These examples and activities are a small subset of the extensive research efforts at the NEHI agencies. This document addresses the NEHI Working Group's broader efforts in coordination, implementation, and social outreach in nanoEHS, as identified in the 2011 NNI EHS Research Strategy. As the NNI agencies sustain a robust budget for EHS research, Federal agencies will continue to invest in tools and share information essential to assess and manage potential risks of current and anticipated ENMs and nanotechnology-enabled products throughout their life cycles. The agencies will also continue to engage with the stakeholder community to establish a broad EHS knowledge base in support of regulatory decision making and responsible development of nanotechnology.

Introduction and Overview

The National Nanotechnology Initiative (NNI) is the U.S. Federal Government's interagency program for coordinating research and development as well as enhancing communication and collaborative activities in nanoscale science, engineering, and technology (see www.nano.gov). The Nanoscale Science, Engineering, and Technology (NSET) Subcommittee is the interagency body responsible for coordinating, planning, implementing, and reviewing the NNI. The Nanotechnology Environmental and Health Implications (NEHI) Working Group, formed by the NSET Subcommittee in 2005, is charged with supporting Federal activities to protect public health and the environment with respect to nanotechnology research and development (see www.nano.gov/NEHI). In October 2011, NSET released the NNI Environmental, Health, and Safety Research Strategy (*1*) that was developed by the NEHI Working Group and hereafter is referred to as the 2011 NNI EHS Research Strategy. Successful realization of the vision of the 2011 NNI EHS Research Strategy—*a future in which responsible development of nanotechnology provides maximum benefit to the environment and to human social and economic well-being*—requires committed interagency implementation of the 2011 NNI EHS Research Strategy. To this end, the NEHI Working Group has produced this progress review of federally funded nanoEHS research. It is noteworthy that robust Federal agency participation in nanoEHS activities is reflected by the continuing strong investment in EHS research, with over $110 million budgeted for the last several years (*2*) despite considerable fiscal challenges and constraints.

The NSET agencies that are actively involved in the NEHI Working Group are the Consumer Product Safety Commission (CPSC), the Environmental Protection Agency (EPA), the U.S. Army Engineer Research and Development Center (DOD/ERDC), the Food and Drug Administration (DHHS/FDA), the National Cancer Institute (DHHS/NIH/NCI) and the National Institute of Environmental Health Sciences (DHHS/NIH/NIEHS) (which jointly represent the NIH), the National Institute of Food and Agriculture (USDA/NIFA), the National Institute for Occupational Safety and Health (DHHS/CDC/NIOSH), the National Science Foundation (NSF), the National Institute of Standards and Technology (DOC/NIST), the Occupational Safety and Health Administration (DOL/OSHA), and the U.S. Geological Survey (DOI/USGS). These agencies have nanoEHS efforts (intramural, extramural, or both) aligned with their missions. The NEHI Working Group requested that each of these agencies identify, for the period FY 2009 to FY 2012, examples of significant research activities. These examples of current, ongoing, and anticipated activities are aligned with the 2011 NNI EHS Research Strategy's six core research areas and corresponding research needs (RNs) as listed in Appendix A. These core research areas are:

- Nanomaterial Measurement Infrastructure (NMI).
- Human Exposure Assessment (HEA).
- Human Health (HH).
- Environment (ENV).
- Risk Assessment and Risk Management Methods (RAMM).
- Informatics and Modeling (IM).

In the 2011 NNI EHS Research Strategy, ethical, legal, and societal implications (ELSI) of nanoEHS research are woven throughout the core research areas to inform research planning and data and product management at all levels. ELSI considerations are treated in a similar manner in this document. Examples of significant NEHI agency and interagency activities and outputs for the RNs in each of the six core research areas are described in this document; the NEHI agencies have many other research activities and outputs that are not included in this document. These six areas are strongly interrelated and synergistic, as shown in Figure 1; however, for simplicity, examples related to multiple core research areas are included under the single area to which each such example most closely pertains.

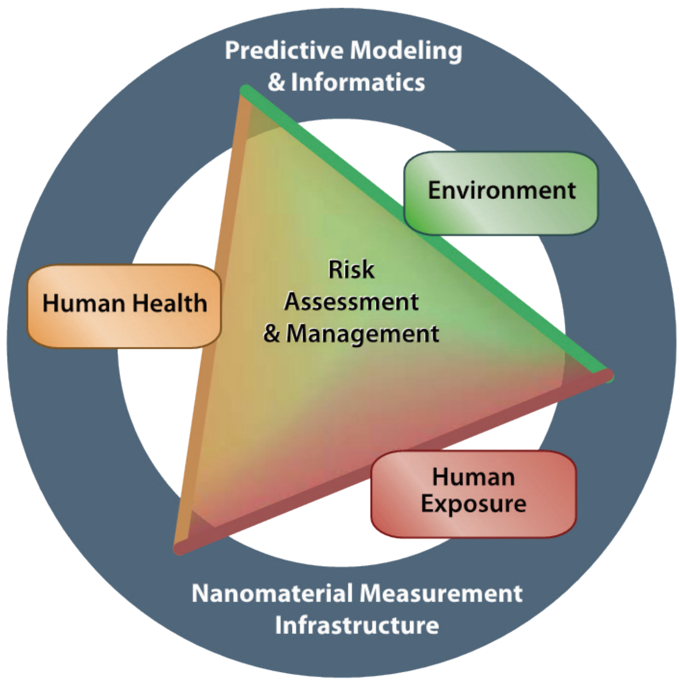

Figure 1. Interrelationship of core research areas of the 2011 NNI EHS Research Strategy.
Source: Debra Kaiser, NIST. N.R. Fuller of Sayo-Art provided revised image graphics.

Consistent with the 2011 NNI EHS Research Strategy, this EHS research progress review utilizes two key terms: (a) *engineered nanomaterials* (*ENMs*), defined as those materials that have been purposely synthesized or manufactured to have at least one external dimension of approximately 1–100 nanometers (nm)—at the nanoscale—and that exhibit unique properties determined by this size; and (b) *nanotechnology-enabled products* (*NEPs*), defined as intermediate engineered nanoscale products, including ENMs embedded in matrix materials, that exist during manufacture and in final products. Other acronyms and abbreviations used throughout this document are presented in Appendix B.

The following six sections of this document contain illustrative examples of NEHI agency intramural and extramural research in each of the RNs for the six core research areas, with an emphasis on interagency collaborations. Collectively, the NEHI participating agencies and the academic grantees supported by several of the agencies have generated over 400 nanoEHS-related publications for the period FY 2009 to FY 2012; only a small number of these publications are referenced herein. Interagency agreements are another way to gauge the level of coordination among the NEHI agencies; CPSC alone has established 19 such agreements on nanoEHS research, some of which are noted herein. Co-sponsored workshops, joint and parallel solicitations, and jointly operated facilities are other mechanisms that demonstrate interagency coordination. Some of the NEHI agencies, individually and in collaboration with other agencies, have provided funding for the establishment of university-based centers, databases, and information platforms; it is critical that investments are made to maintain and, if warranted, grow such important entities. Two of the largest centers, the Center for the Environmental Implications of Nanotechnology (CEIN) and the Center for the Environmental Implications of NanoTechnology (CEINT), were established in 2008 and are jointly funded by NSF and EPA through NSF cooperative agreements (*3*). Research in these two centers is cited extensively throughout this document.

The section of this review document entitled *Implementation and Coordination of the 2011 NNI EHS Research Strategy* describes the NEHI Working Group's efforts in international coordination of NNI EHS research and standards, improvement of internal operations, support for regulatory decision making and industry partnerships, and increasing communication with stakeholders. Appendix C summarizes the scope of the nanoEHS-related research centers and facilities supported by the NEHI participating agencies, and Appendix D provides references for the specific research examples described in this document.

The NEHI Working Group recognizes the value and importance of periodic reviews of the Federal Government's nanoEHS research strategy. Reports ensuing from such reviews have been published in recent years by the President's Council of Advisors on Science and Technology (*4*), the National Research Council (NRC) of the National Academies (*5*), and the Government Accountability Office (*6*). This nanoEHS progress review is responsive to recommendations in such past reports and provides stakeholders with relevant information concerning the nanoEHS research and coordination activities of the NEHI Working Group and its participating agencies. It should be noted that this progress review of NNI EHS research covers the period FY 2009 to FY 2012 and was prepared prior to the September 2013 release of the NRC report *Research Progress on Environmental, Health, and Safety Aspects of Engineered Nanomaterials* (*7*). That NRC report assessed progress over a brief period towards the NRC's suggested approach, whereas the present document describes specific Federal agency activities and related outcomes that address the research needs articulated in the 2011 NNI EHS Research Strategy.

Nanomaterial Measurement Infrastructure

The Nanomaterial Measurement Infrastructure (NMI) core research area aims to establish a comprehensive set of measurement tools—instruments, protocols and assays, standards, benchmark data, and models—to enable accurate and reproducible measurements of ENMs and NEPs. Research is focused on ENMs with the greatest production volumes and the greatest concern for exposure and hazards, such as carbon nanotubes (CNTs) and silver and titanium dioxide (TiO_2) nanoparticles (NPs), and NEPs in widespread use, including nanosilver in textiles and multiwalled CNTs (MWCNTs) in polymer composites. The five NMI-RNs described below address the full life cycle of ENMs and NEPs in all relevant media, e.g., soil, water, blood, and tissue. Considerable progress in research and interagency collaboration has been achieved over the period FY 2009–FY 2012; research examples are presented here.

NMI-1: Develop measurement tools for determination of physico-chemical properties of ENMs in relevant media and during the life cycles of ENMs and NEPs

Physico-chemical tool development, led primarily by NIST with contributions from NIOSH, NSF, EPA, FDA, and the National Cancer Institute's Nanotechnology Characterization Laboratory (NCI/NCL), has focused on physical dimensions, surface properties, and dispersion properties of ENMs. NIST, with key contributions from NCI/NCL and NIOSH, has generated reference materials, associated protocols, and data for measurements of surface area (for nanoscale TiO_2), size (for single-walled CNTs [SWCNTs] and gold NPs), and composition (for SWCNTs and catalyst mixtures) (*8*). Over 1,000 units of NIST's nanoscale reference materials have been sold in nearly equal numbers to domestic and international organizations, of which 45% were industrial and 43% were government agencies. Reference materials are essential for instrument calibration (*9*) and have been used in interlaboratory studies involving EPA, FDA, NIOSH, and NCI/NCL. Researchers from NIOSH, NIST, and other national metrology institutes have published a perspective article on reference materials for EHS measurements (*10*). Instrumentation advances, led by NIST, have included "hyphenated" instruments consisting of two or more coupled commercial instruments for simultaneous measurement of two or more properties, such as size and surface composition (*11*). NIST and NCI/NCL have jointly developed five protocols for NP size determination (*12*): the dynamic light scattering and atomic force microscopy protocols were the basis for consensus standards by ASTM International's Technical Committee E56 on Nanotechnology (ASTM E56) (*13*); and the dynamic light scattering protocol was adopted by the International Alliance for NanoEHS Harmonization (IANH) (*14*). Collaboration between NIST and CEINT has resulted in five protocols on the dispersion of nanoscale TiO_2 in various media (*15*). These protocols have been incorporated into the Organisation for Economic Co-operation and Development's (OECD) Programme for Testing of Manufactured Nanomaterials (*16*). In consultation with NCI/NCL, FDA established two Nanotechnology Core Facilities: one located at the FDA's Jefferson Laboratories, the home for FDA's National Center for Toxicological Research and Office of Regulatory Affairs Arkansas Regional Laboratory, and the other at FDA's White Oak Facility (see www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofScientificandMedicalPrograms/NCTR/default.htm). Since their establishment, these facilities have been used to train FDA staff and for research by FDA and NIEHS grantees; future plans include their use in collaboration with other NEHI agencies. Finally, with leadership and contributions from NIST, NIOSH, and FDA, more than 15 consensus standards concerning physico-chemical property measurements have been developed by ISO Technical Committee 229 on Nanotechnologies (ISO/TC 229) (*17*) and ASTM E56.

NMI-2: Develop measurement tools for detection and monitoring of ENMs in realistic exposure media and conditions during the life cycles of ENMs and NEPs

Many of the NEHI agencies have worked on the development of tools for sampling and collecting ENMs, detecting the presence of ENMs in various media and in NEPs, and quantifying ENM concentration. In collaboration with NIEHS, NIST, ERDC, the Air Force Research Laboratory (AFRL), and private sector stakeholders, NIOSH has led an effort to develop methods for evaluating worker exposure using a multimetric approach that includes mass, particle number, size distribution, and surface area (*18*, *19*). NIOSH also led the development and licensing of a new type of portable, direct-reading instrument for the detection of airborne ENMs, and it continues to evaluate the use of ultrafine aerosol sampling methods and devices to evaluate personal breathing zone exposures to ENMs in workplace settings (*20*). Further, NIOSH has conducted ENM air-sampling assessments at about 40 research and industrial facilities, including laboratories at NIST, NIEHS, and ERDC. ENM size, size distribution, and other exposure parameters in air have been characterized by NIOSH (*21*). In collaboration with FDA, NIST has developed a fluorescently labeled silicon NP reference material to be released in summer 2014 (*22*). Since 2011, CPSC and NIST have jointly conducted research on instruments and protocols to collect and characterize NPs released into the air by various means such as mechanical abrasion (*23*). Extramural research projects at universities supported by ERDC, NSF, and EPA have focused on methods for detecting ENMs in environmental media (*24*) and on sensor-based tools for real-time characterization of the concentration and size distribution of ENMs in such media (*25*). A joint solicitation by EPA, CPSC, and the UK Environmental Nanoscience Initiative has resulted in the development of methods to detect, assess, and monitor the presence of ENMs in biological and environmental samples (*26*).

NMI-3: Develop measurement tools for evaluation of transformations of ENMs in relevant media and during the life cycles of ENMs and NEPs

The lead agencies conducting or funding research on ENM transformations are EPA, NSF, and NIST, with contributions from CPSC, FDA, ERDC, NIEHS, and NCI/NCL. Dissolution, agglomeration, and aggregation are the most widely studied types of transformations. Benchmark data for various ENMs in air, aqueous-based environmental solutions, and biological fluids constitute key measurements reported for NMI-3. An extensive list of publications on tools for studying ENM transformations is available on the CEINT website (see www.ceint.duke.edu/biblio). EPA has published results on transformations of various ENMs in air (*27*). Joint research between EPA and NIST has elucidated the effects of agglomeration state and dispersion of silver NPs on NP size measurements in environmentally relevant media (*28*). NIST has generated benchmark data on the dissolution of silver NPs in environmental and biological matrices (*29*) as a prelude to the development of forthcoming silver reference materials, the requirements of which were established through discussions with EPA, ERDC, FDA, and NIOSH. Several of the NEHI agencies have published studies on aggregation of various

ENMs (*30*, *31*). FDA and NIST jointly conducted a study on absorption and conformation of bovine serum albumin on gold NPs (*32*). Through an interagency agreement with CPSC, NIOSH has evaluated the dissolution of silver from silver nanoparticles incorporated into commercially available textile products using artificial biological fluids and has modeled speciation (*33*).

NMI-4: Develop measurement tools for evaluation of biological responses to ENMs and NEPs in relevant media and during the life cycles of ENMs and NEPs

NIEHS, NCI/NCL, FDA/NCTR, NIOSH, EPA, and NIST have collaborated with academic institutions, supported in part by NSF, and with international organizations to assess the applicability of existing toxicity assays to ENMs (*34*) and to develop new toxicity assays. These collaborations have resulted in a large number of *in vitro* and *in vivo* assays that have been used to study all classes of ENMs (including metals, metal oxides, carbon-based, and quantum dots). Notably, NCI/NCL has reported 30 *in vitro* assays applicable to multiple types of ENMs (*12*). NIST gold reference materials have been used in a number of studies to generate validated toxicity (*35*) and biological exposure data (*36*). The design of quantitative assay "arrays" with controls and quality metrics that enhance assay performance and improve robustness is an ongoing effort at NIST. Recent efforts from CPSC, in collaboration with CEINT, have focused on developing innovative tools for measuring the potential health impacts of nanotechnologies used in the flame-retardant treatment of thermoplastic- and thermoset-based consumer products (*37*). Finally, ISO/TC 229 and ASTM E56, with leadership and contributions from the NEHI agencies, have issued consensus standards concerning the biological responses of cells and animal models to various ENMs (*38–40*) (these standards can be found online on the ASTM and ISO websites by searching for "nanotechnology").

NMI-5: Develop measurement tools for evaluation of release mechanisms of ENMs from NEPs in relevant media and during the life cycles of NEPs

With increasing incorporation of ENMs in NEPs, measurement tools are urgently needed to quantify the release of ENMs from NEPs for risk assessment and management. NMI-5 was newly defined in the 2011 NNI EHS Research Strategy, and NEHI agency activities in this RN have been increasing since FY 2009. NIOSH and NIST have generated protocols and data on the release of ENMs with partial funding by and in collaboration with CPSC (*41–43*). The primary release mechanisms in these studies are incineration (*44*), mechanical degradation (*23*), photo-induced and hydrolytic degradation (*45*), and consumer interactions such as spraying ENMs (*46*, *47*) and mouthing and swallowing NEPs. ENMs that have been measured in these release studies include silver and metal oxide NPs, CNTs, and nanoclays. In the International Life Sciences Institute (ILSI) NanoRelease Consumer Products Project (*48*), CPSC, EPA, OSHA, NIST, and NSF have been collaborating with U.S. industry and not-for-profit organizations, and with Canadian and EU government agencies and industry, to identify and develop methods to detect, quantify, and characterize MWCNTs that are released from MWCNT-polymer composite consumer NEPs by mechanical degradation and weathering, e.g., exposure to light and water.

Human Exposure Assessment

The Human Exposure Assessment (HEA) core research area outlines the research needed to understand the potential exposure of humans to key classes of ENMs (i.e., metal oxide, metal, and carbon-based) and NEPs. Data generated by the four HEA-RNs below will contribute to control strategies that will minimize exposures. As may be expected given their environmental and occupational safety and health missions, EPA and NIOSH are the leaders in this research area, although other NEHI participating agencies, primarily NSF, NIEHS, CPSC, and OSHA, also contribute through intramural research and external grants. Global partnerships have been formed, most notably with research groups in the United Kingdom (UK Environmental Nanosciences Initiative, www.nerc.ac.uk/research/funded/programmes/nanoscience) and in TNO (a Dutch nonprofit organization for applied scientific research, www.tno.nl/index.cfm?Taal=2). A highlight in the HEA research area is the cohort of more than 40 site investigations performed by NIOSH during FY 2009–FY 2012 (as mentioned in the NMI section) to assess exposure to several types of ENMs in various laboratory and industrial settings. Specific examples of research activities are described below for each HEA-RN.

HEA-1: Understand processes and factors that determine exposures to nanomaterials

EPA, NSF, and NIOSH, with mission-specific assistance from OSHA, conduct and fund activities aimed at understanding the processes through which exposure to ENMs might occur. For example, EPA and UK researchers are assessing public exposure to the fuel additive nanoscale cerium oxide (*49*) when it is released into the air. EPA has also developed a Comprehensive Environmental Assessment (*50*) tool for ENMs that evaluates exposure and hazard to NEPs. NIOSH exposure studies, some conducted in collaboration with NIEHS (*51*) and CPSC (*33*), focus on measurements in the workplace and include characterizing the determinants of exposure as they relate to processes and tasks. Predictive modeling of ENM exposures is supported by the EPA's ToxCast™ Program (*52*) and at CEINT and CEIN, which are jointly supported by NSF and EPA. NIOSH organized a *Safe Nano Design* workshop in August 2012 (*53*) to explore the identification of design principles that would minimize exposures to and hazards of ENMs. OSHA has funded the development of a student guide on ENMs and occupational safety and health (*54*), and has collected a compendium of resources on workplace exposure control methods for ENMs (*55*). On an international level, numerous NEHI agencies, notably OSHA and NIOSH, participate in efforts to harmonize exposure measurement methods. For example, NIOSH is a co-leader of the Global Exposure Measurements Harmonization Workgroup that is developing standard operating procedures for the collection and sharing of exposure measurement methods and data for ENMs (*56*).

HEA-2: Identify population groups exposed to engineered nanomaterials

Consumers and workers are the two populations most likely to be exposed to ENMs. There are substantive efforts supported by CPSC (see the interagency agreements cited earlier) to quantify potential exposures and health impacts of ENMs in consumer NEPs. For example, silver NPs, mainly used as anti-odor and disinfectant agents, are found in aerosol sprays and textile coatings, and CNTs are used in sports equipment and in a range of materials as flame retardants (*57*). EPA was involved in the identification of potential life cycle scenarios for the release of MWCNTs from MWCNT-polymer composite consumer NEPs as part of the NanoRelease Consumer Products Project mentioned earlier. New strategies to track ENMs in the environment, including biodistribution in plant and animal species, are under development at CEINT (*58*). NIOSH and NIEHS are coordinating research on exposure and health studies in the workplace (*51*), for example, an epidemiologic study of carbon nanotube workers (*59*) that also includes preliminary work on biomarkers (*60*). Joint research at FDA and CPSC is aimed at assessing potential consumer exposures to ENMs used in commercial products that come into contact with foods (*61*). Additional efforts to detect, characterize, and evaluate ENMs released from food is being coordinated as part of the NanoRelease Food Additive Project (*62*). Research on potential exposures of consumers to ENMs released from clothing is jointly supported by CPSC and NSF (*63*). In January 2013, NIEHS conducted a workshop with participation of NIOSH, CPSC, and NIEHS-funded extramural investigators to identify research issues and promote development of sensors for personal nanoparticle exposure monitoring devices (*64*). At this meeting, NIEHS also examined the feasibility of performing epidemiological studies for groups in the general population that have been using commercially available NEPs.

HEA-3: Characterize individual exposures to nanomaterials

NIOSH, with support from NIEHS, is collecting personal, integrated field samples to expand its knowledge of nanomaterial exposure and is developing expanded transmission electron, scanning electron, and hyperspectral microscopy capabilities to support that effort. NEHI agencies are working together to establish critical linkages between exposure characterization and fate, transport, and biological impact research. EPA and CPSC are jointly conducting research on exposure assessment of silver NPs in NEPs (*65*). EPA, NIOSH, and NIEHS have also participated in the development of globally consistent standard operating procedures for exposure assessment, notably with research groups in the UK and TNO. Research on inhalation exposures of ENMs in cosmetics has been supported by NIEHS (*66*).

HEA-4: Conduct health surveillance of exposed populations

The exposure measurement and hazard assessment tools necessary for meaningful health surveillance of exposed populations have been the focus of several research programs, and the success of these programs is now enabling progress in the development of health surveillance methods. With input from a stakeholder workshop on health surveillance in the nanotechnology workplace (*67*), NIOSH and university collaborators have developed a roadmap towards a framework for health surveillance and epidemiology of ENM workers (*68*). The previously mentioned *NIEHS Nano Exposure Workshop* (*64*) also focused on the status of the science for epidemiological studies in populations exposed to ENMs, including the roles of physician case reports and injury and illness reports.

Human Health

The Human Health (HH) core research area consists of six interrelated RNs that together aim to further an understanding of the modes of interaction between ENMs and human biology. The research includes investigations of toxicology, human susceptibility, and the physico-chemical properties of ENMs as they relate to biological absorption, distribution, metabolism, and excretion (ADME) of these materials. Efforts to identify appropriate and reproducible assays that allow reliable data generation and sharing are successfully propelling human health research teams forward. This section provides examples of research that addresses the six HH-RNs at both the national and international levels. As may be expected given their health and biology missions, NIEHS, NCI/NCL, NIOSH, and NSF are the leaders in conducting and supporting HH research, although other NEHI are strong contributors. For example, OSHA, recognizing the need to collate and organize research findings, is developing a health effects database of peer-reviewed publications across a wide spectrum of biological endpoints.

HH-1: Identify or develop appropriate, reliable, and reproducible *in vitro* and *in vivo* assays and models to predict *in vivo* human responses to ENMs

NIEHS, NCI/NCL, NSF, EPA, and NIOSH are the primary research agencies contributing to the development of reliable assays and methods that characterize and quantify acute and chronic toxicity and link *in vitro* measurements to *in vivo* responses. NIEHS supported the Engineered Nanomaterials Grand Opportunity (Nano GO) consortium (*69*) involving numerous institutions for the development of standardized protocols (*70*, *71*). A perspective article co-authored by EPA, NIOSH, OSHA, CEIN, and industrial researchers concerns the use of alternative test strategies to reduce reliance on animal testing; such strategies include *in vitro* and *in silico* methods such as high-throughput screening and computational modeling (*72*). Integrated testing approaches developed by CEIN are leading to high- and moderate-throughput screening tools as well as quantitative structure-activity relationships and predictive models (*73*, *74*). FDA and NCI/NCL are coordinating on safety and efficacy assessments of mission-related ENMs and nanotechnology-enabled devices. The information from such assessments contributes to the broad understanding of ENM toxicity (*75*, *76*). At the close of 2011, NCI/NCL reported 30 assays for *in vitro* measurements of ENMs (*12*). NIOSH has developed methods for CNT and carbon nanofiber (CNF) toxicity determination (*77*), with broad support from NIEHS and CPSC. In conjunction with four other national measurement institutes, NIST is developing robust *in vitro* cytotoxicity assays and conducting interlaboratory tests on ENMs using these assays. EPA and other NEHI agencies are the Lead Sponsor or Lead Co-Sponsor for the safety testing of six ENMs in the OECD Sponsorship Programme, which includes methods to assess toxicity (*78*).

HH-2: Quantify and characterize ENMs in exposure matrices and biological matrices

NEHI agencies support research to characterize ENMs at the molecular, cellular, tissue, and whole animal levels in biological matrices derived from the skin, lung, cardiovascular system, central nervous system, and digestive tract. The quantification and assessment of ENMs includes physico-chemical property measurements (e.g., size distribution and concentration) and quantitative pathology investigations. Researchers at AFRL and NIEHS are developing quantitative analytical tools to measure key parameters of ENMs in biological systems (*79*, *80*). NIOSH, with NIST and CPSC, has made significant advances in understanding ENMs in exposure matrices such as workplace and product surfaces and is performing relevant supporting studies in rodent models (*81*). EPA, in collaboration with the UK, supports academic research on the concentration, characteristics, and toxicity of particles emitted from combustion engines using nanoscale cerium oxide-doped diesel fuel (*82*). Collectively, these programs have advanced the quantification and characterization of exposure and exposure measurement techniques and provide the foundation for development of biomarkers of exposure.

HH-3: Understand the relationship between the physico-chemical properties of ENMs and their transport, distribution, metabolism, excretion, and body burden in the human body

The findings on relationships between the physico-chemical properties of ENMs and their transport and ADME in the human body provide critical information about the type and extent of biological responses. EPA, NIEHS, and NIOSH coordinate research activities using comparative physiological approaches and *in vitro* methods to examine differences in the bioavailability and the behavior of functionalized ENMs in the human body (*83*). NIEHS is funding the development of biomarkers as indicators of toxicological response (*84*), as well as computational models to predict toxicity of silver and carbon nanoparticles (*85*). NSF and EPA jointly fund studies that use alternative models to determine relationships between toxicity and physico-chemical properties; one example is zebrafish assay research at CEIN on diverse ENMs such as metal and metal oxide NPs and CNTs (*86*). Scientists at AFRL use state-of-the-art physico-chemical characterization, determination of appropriate exposure protocols, and reliable methods for assessing ENM uptake and their kinetics in living organisms (*87*). NIFA supports research on the fate and transport of ingested ENMs (*88*). CEINT has published a comprehensive article on the effects of physico-chemical properties of ENMs on biological activity (*89*).

HH-4: Understand the relationship between the physico-chemical properties of ENMs and uptake through the human port-of-entry tissues

Deciphering the process through which ENMs enter the body is critical to risk assessment and risk management, and significant research efforts by the NEHI agencies have focused on pulmonary and dermal uptake at the cellular and organ-system levels. Current efforts build on these findings and explore ENM uptake in multiple species through multiple exposure routes. For example, the NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR) Consortium (*90*, *91*) was established in 2010 to support efforts to understand how physico-chemical characteristics of ENMs influence their interactions with biological systems and how these effects impact human health. In 2012, NIEHS launched an intramural Nanotechnology Safety Initiative (*92*) with the goal of determining relationships of physico-chemical and toxicological properties in major classes of ENMs, e.g., metal and metal oxide NPs and CNTs. NIFA has funded research on the impact of physico-chemical properties on cellular uptake and potential toxicity of ENMs as food additives (*93*). FDA has joint publications on dermal penetration of ENMs with NCI/NCL (*94*) and NIEHS (*95*). While most reported toxicity studies employ an acute exposure paradigm, NIOSH is performing chronic pulmonary CNT exposure studies with post-exposure evaluation periods as long as seventeen months (*96*) and with endpoints in multiple organ systems including lung, heart, brain, liver, spleen, and kidney (*97*). Innovative inhalation research in an academic-industrial manufacturing environment is being supported by NSF; the goal is to quantitatively assess the relationships between *in vitro* nanotoxicity and physico-chemical characteristics of CNTs and CNFs (*98*).

HH-5: Determine the modes of action underlying the human biological response to ENMs at the molecular, cellular, tissue, organ, and whole body levels

Mode-of-action studies, i.e., research to understand the biological mechanisms underlying the human health response to ENMs, utilize and extend research in the previous RNs. Intramural and extramural research programs at NIEHS, NCI/NCL, NIFA, ERDC, AFRL, EPA, and NSF incorporate dose–response metrics and elements of mode-of-action research into exposure, fate, and transport studies in *in vitro* and *in vivo* systems. For example, NIEHS and EPA are collaborating on mode-of-action studies, one research area in the broader NIEHS intramural NanoHealth Signature Program (*99*). These programs also include fundamental studies of the molecular interactions between ENMs and biological membranes and research on ENM-protein interactions. AFRL has published research on biological responses to nanoenergetic materials such as nanoscale aluminum (*100*, *101*). NIOSH is employing *in vitro* assays to query CNT-induced transformation of lung epithelial cells (*102*) and is evaluating the cardiovascular response to pulmonary exposure to ENMs, with partial support from CPSC (*103*). The moderate- and high-throughput screening technologies developed by CEIN and CEINT (*73*, *89*) will be critical for understanding biological activity as well as correlating *in vitro* to *in vivo* biological responses. Another research effort supported by NIEHS and conducted at CEIN concerns the development of biomarkers as indicators of toxicological response (*84*).

HH-6: Determine the extent to which life stage and/or susceptibility factors modulate health effects associated with exposure to ENMs and nanotechnology-enabled products and applications

The effects of life-stage and susceptibility factors on human health and environmental impacts of ENMs are most well-aligned to the missions of NIEHS and EPA. Several components of the NCNHIR Consortium are investigating ENM exposure during pregnancy, lactation, disease states such as asthma and emphysema, and altered physiology such as the antibiotic-treated digestive tract (*104*). EPA is supporting research to identify key factors, including environmental factors that may cause sub-populations to be more susceptible to adverse health effects of ENMs.

Environment

The overarching aim of the Environment (ENV) core research area is to characterize the transport and transformation of ENMs entering various environmental media during all stages of ENM and NEP life cycles. Information concerning the mode of entry of ENMs into the environment; changes in composition, size, and morphology of ENMs; and the mechanisms of interaction of ENMs with both biotic and abiotic substances in the environment will enable comprehensive assessments of environmental impacts. Such assessments will yield more accurate data on exposure levels, a more conclusive understanding of the state of an ENM involved in an actual exposure, and more precise information on the location at which the exposure occurs. EPA, NSF, NIEHS, NIOSH, and NIST are the leaders in conducting and supporting research in the five ENV-RNs listed below; CPSC, USGS, and NIFA have also contributed to the ENV core research area.

ENV-1: Understand environmental exposures through the identification of principal sources of exposure and exposure routes

Exposure identification, measurement, and modeling are essential to understanding the type and magnitude of an ENM exposure. The NSF Center for Biological and Environmental Nanotechnology (CBEN) (*105*, *106*), CEIN (*107*), and CEINT (*108*) have addressed exposure issues through evaluation of the impact of an exposure on environmental receptors in simulated mesocosms and terrestrial ecosystems, and through the development of a web-based multimedia model of environmental release and subsequent distribution of ENMs. NIST reported the results of a pilot estuarine mesocosm study on the environmental fate of silver NPs leached from NEPs (*109*). EPA and CPSC have joint research aimed at prioritizing environmental exposure potential for NEPs and at estimating and predicting potential entry exposure pathways (*110*). A review article on potential exposure pathways for CNTs has been published by NIST (*111*).

ENV-2: Determine factors affecting the environmental transport of nanomaterials

The transport of ENMs through the environment is determined, in part, by the physico-chemical properties of ENMs and environmental characteristics. Research at several NEHI agencies has shown that the presence of natural organic matter (NOM), sulfur, and chlorides impacts environmental transport of silver NPs. For example, NIST has completed a prototype study (*112*) demonstrating the use of stable isotopes to probe interactions between NOM-coated silver NPs and a NIST estuarine sediment standard reference material (*113*).

Research is ongoing at EPA (*114*) and CEINT (*115*) to identify the factors that control the stability and mobility of ENMs in aqueous, atmospheric, and land ecosystems, including transition areas such as wetlands; metal and metal oxide NPs and carbon-based nanomaterials such as CNTs serve as the primary test materials. CEINT has reported the relationship between ENM aggregation and transport in environmental systems (*116*). The fate of nanoscale aluminum oxide, a material with potential widespread dispersal in soil systems, has been investigated by ERDC (*117*). CEINT researchers are also developing a framework for environmental ENM risk assessment that includes critical ENM–ecosystem interactions and a robust platform for modeling ENM structure–activity relationships (*118*).

ENV-3: Understand the transformation of nanomaterials under different environmental conditions

Research at several NEHI agencies focuses on identifying environmental processes that cause changes in aggregation state, solubility, or coating and capping of ENMs that may alter toxicity and bioavailability. For example, research studies have indicated that silver NPs in an environment exhibiting elevated concentrations of chlorides is transformed to silver chloride, a chemical form with decreased bioavailability compared to silver (*119*). Intramural research at EPA and extramural research at CEINT are ongoing to determine linkages between ENM physico-chemical properties and ENM transformations in ecosystems and to identify the factors that control biotransformation and bioavailability of CNTs and fullerenes in water and soil (*120*). Researchers at CEINT have published a review article on transformations of ENMs after they enter the environment (*121*). ERDC has reported research on the effect of organic solutes on the dispersion of silver NPs (*122*); USGS is determining the potential for dissolved organic matter to alter ENM toxicity and impact on bacteria; and NIFA is studying transformations of ENMs in soil. Research at EPA has focused on analytical approaches to measure changes in the properties of metal and metal oxide NPs in aqueous media and in water treatment processes (*119*, *123*, *124*).

ENV-4: Understand the effects of engineered nanomaterials on individuals of a species and the applicability of testing schemes to measure effects

Dose–response characterization and mode-of-action studies are critical to understanding the impact of ENMs on species in aquatic, estuarine, and terrestrial ecosystems; NEHI agencies are conducting and funding research for all of these ecosystems. NIOSH, EPA, and NSF are coordinating research to develop medium- and high-throughput dose–response quantification tools that will provide data for the development of hazard ranking methods, test guidelines, and predictive models in environmental systems (*74*). Extramural and intramural programs funded by NSF and EPA include mode-of-action studies for model invertebrates (*Daphnia*, bacteria, insects), vertebrates (fish, mice), and plants (*125*). NIST has published a review article on methods to measure ecotoxicity of CNTs (*126*). The effects of organic carbon on the ecotoxicity of silver NPs have been reported by ERDC (*127*). Studies on the effects of ENMs in agricultural settings have been funded by NIFA (*128*). USGS has conducted research on the bioavailability and toxicity of various ENMs on flora and fauna: for example, ecotoxicity in higher plant species resulting from gallium and indium NPs released during recycling of electronic devices (*129*); the potential of isotopically modified ZnO NPs to serve as environmental tracers (*130*); and bioaccumulation, bioactivity, and toxicity of silver NPs ingested by freshwater snails (*131*).

ENV-5: Evaluate the effects of engineered nanomaterials at the population, community, and ecosystem levels

Environmental research at the level of an individual within a species will critically inform research on the effects of ENMs in populations and communities. CEIN is conducting research on the effects of ENMs on reproduction, growth, and survival of organisms to predict impacts on ecosystem populations and communities (*107*). Ongoing research at CEINT focuses on bioaccumulation of ENMs in the environment and the food web (*132*). NIFA has funded a number of universities to study the use of ENMs in food and agriculture; one such study focuses on the impact, detection, and tracking of NPs in crops and associated soil microbes (*133*). NSF supports research on the ecological impacts of nanomanufacturing in areas such as telecommunications, health care, energy, and security. For example, research is underway (*134*) to determine specific environmental impacts such as those associated with nanoscale lithium compounds discharged from batteries disposed of in landfills (*135*).

Risk Assessment and Risk Management Methods

The Risk Assessment and Risk Management Methods (RAMM) core research area outlines the research needed to develop comprehensive principles for establishing robust risk assessment and risk management practices for ENMs and approaches for identifying, characterizing, and communicating risks to all stakeholders. Development of such principles requires integration of information obtained from research and related activities in the four core research areas described previously—measurement, exposure assessment, human health, and the environment—and incorporation of predictive models across NEP life cycles. A key NNI workshop that informed agency research in RAMM was the 2010 *Capstone Meeting: Risk Management Methods and Ethical, Legal, and Societal Implications of Nanotechnology* (*136*). The *2013 NNI workshop on the Perception, Assessment, and Management of the Potential Risks of Nanotechnology* (*137*), for which planning began in 2012, provided NEHI agencies with invaluable perspectives on the perception, assessment, and management of ENM risks. Examples of other relevant agency activities and research focused on potential risks in the workplace, to consumers, and to the environment are presented in the five RAMM-RNs listed below.

RAMM-1: Incorporate relevant risk characterization information, hazard identification, exposure science, and risk modeling and assessment methods into the safety evaluation of nanomaterials

NEHI agencies are engaged in research and related activities to characterize potential exposures and biological impacts across the life cycles of ENMs and NEPs. For example, NIOSH has published an article that provides a state-of-the-art overview on utilizing current hazard research data and risk assessment methods for ENMs to develop and implement effective risk management guidance (*138*). Ongoing activities have focused on using an evidence-based strategy to develop occupational exposure limits (OELs) for various ENMs (*139*); OSHA has published a *Working Safely with Nanomaterials* fact sheet that addresses OELs (*140*). Additionally, a workshop entitled *Strategies for Setting Occupational Exposure Limits for Engineered Nanomaterials*, held in September 2012, brought together occupational health leaders from academia, government, industry, and nongovernmental organizations; the workshop report (*141*) was co-authored by scientists from OSHA, NIOSH, and EPA. Quantitative exposure and hazard data from all the NEHI agencies are being integrated into risk assessment models to estimate risks to public health and the environment and into *in silico* models that could lead to tools to predict ENM behavior across NEP life cycles. For example, CPSC and NSF are jointly supporting research at CEINT to develop risk models for human exposure to ENMs released from NEPs (*37*). This research effort is part of a broader collaboration involving NIST, CPSC, CEINT, and CEIN on the release, exposure, and health impacts of ENMs incorporated into NEPs and on *in vitro* and *in silico* methods that will identify potential health risks (*142*). A multistakeholder workshop involving some of the NEHI agencies evaluated the potential use of alternative testing strategy data (e.g., *in vitro* and limited *in vivo* data in a tiered testing scheme) in hazard assessment and toxicity prediction of ENMs (*72*). Other NEHI agencies such as EPA (*143*) and FDA (*144*) have targeted efforts to evaluate risk characterization information for products that may contain ENMs or otherwise involve the application of nanotechnology. Through international organizations such as OECD and ISO, NEHI agencies are partnering with countries or regions to share approaches, develop strategies, and study potential risk management approaches across the life cycles of ENMs and NEPs.

RAMM-2: Understand, characterize, and control workplace exposures to nanomaterials

The NEHI agencies continue to develop, refine, and implement methods to measure and control occupational exposures as illustrated by the examples presented in the NMI-2 and HEA-1 sections of this document. In collaboration with several university and private sector partners, NIOSH has developed and disseminated guidance for the safe handling of ENMs in research laboratories that includes containment and control strategies (*20*) and published a comprehensive report entitled *Approaches to Safe Nanotechnology* (*145*). In coordination with CEIN, NIOSH is also compiling data on workplace and environmental exposures to ENMs and NEPs, baseline health indicators, and possible health problems of workers due to such exposures. Additional efforts focus on workplace best practices, including guidance for staff working in academic laboratories and new considerations posed by nanomanufacturing technologies. Integration of this information will support the development of prospective and systematic approaches for occupational risk modeling.

RAMM-3: Integrate life cycle considerations into risk assessment

General insights have been gained about the use of risk assessment data across the life cycles of NEPs, largely through case study analyses that are collaborative in nature and include partners, both domestic and international, from academia, industry, and government agencies. Notably, EPA has developed a Comprehensive Environmental Assessment (CEA) approach (*50*) that integrates life cycle analysis, exposure assessment, hazard analysis, and risk characterization. This approach has been used by EPA in case studies on three ENMs: nanoscale titanium dioxide in water treatment and in topical sunscreens (*146*); nanoscale silver in disinfectant spray (*147*); and multiwalled carbon nanotubes in flame-retardant coatings in upholstery textiles (*148*). CEIN is conducting research on life cycle assessment at the nanoscale (*149*). One goal of a program jointly funded by EPA, CPSC, and the UK (*26*) is to use life cycle analyses to develop integrated models of fate, behavior, bioavailability, and effects for several ENMs over key environmental pathways. In this program, life cycle analyses are being developed for metal and metal oxide NPs and composite ENMs. ERDC is developing methods and tools to integrate life cycle considerations into assessment of the environmental footprints of ENMs (*150*, *151*). The types of life cycle tools and information described above are being used by NEHI agencies whose missions include development and application of risk management methods. Additional work concerns the integration of toxicological characterization results on ENMs during NEP life cycles into risk assessment frameworks.

RAMM-4: Integrate risk assessment into decision-making frameworks for risk management

Current activities focus on the collection of risk-relevant information across a product life cycle on a case-by-case basis, which is the first step in the synthesis of information for development of innovative analytical tools and risk assessment. One example is EPA's CEA approach mentioned above, which provides both a framework for systematically organizing complex risk-relevant information and a process that uses collective judgment to evaluate such information for risk management planning (*152*). NIOSH and EPA, as part of their risk assessment and risk management tool development efforts, are jointly evaluating hazard banding as a method to categorize ENMs by hazard potential (*153*). Articles on the state of ENM risk management and decision making have been published by NIOSH researchers (*138*, *154*). Other NEHI agencies, including CPSC and FDA, incorporate risk assessment approaches on a case-by-case basis when assessing products that may contain ENMs or otherwise involve the application of nanotechnology to inform risk assessment and management. Recent risk assessment activities at ERDC include the development of models based on multicriteria decision analysis and the value-of-information approach for prioritizing nanoEHS research strategies (*155*). Formal decision analysis methods under development include an occupational exposure band tool to assign ENMs to categories (*153*) and a multicriteria decision analysis tool to evaluate different risk metrics for ENMs. NEHI agencies continue to engage with stakeholders in relevant workshops (*156*) on risk analysis and management.

RAMM-5: Integrate and standardize risk communication within the risk management framework

NSF-supported research to develop risk communication models and integrate them into risk management frameworks has been conducted at large university-based research centers where risk communication is a component of larger nanotechnology research programs (*157*). NIOSH, a lead agency in integrating and standardizing risk communication information, is developing risk management guidelines for ENMs in the workplace. CPSC, OSHA, and NSF have used communication tools, guidance documents, and other publicly available documents to disseminate knowledge about products that may contain ENMs or otherwise involve the application of nanotechnology. Information on potential risks of nanotechnology has been communicated to the public at two NNI workshops (*136*, *137*). These workshops also inform agency research in RAMM. The NEHI agencies are developing methods to share early hazard information and terminology for communicating potential ENM risk assessment and management approaches to multiple stakeholders. OSHA has funded the development of a student guide on nanotechnology that includes a module on risk and hazard communication (*54*).

Informatics and Modeling

The Informatics and Modeling (IM) core research area is aimed at enhancing the quality and availability of data; expanding theory, modeling, and simulation capabilities; and building a collaborative informatics infrastructure that will provide data for protection of public health and the environment as well as for research and product development. In the 2011 NNI EHS Research Strategy, only one RN having seven components was identified for the IM core research area, as listed in Appendix C. Recognizing the critical role of data and modeling in ENM development, the NNI agencies selected informatics and modeling as a Nanotechnology Signature Initiative (NSI) focus area (see www.nano.gov/signatureinitiatives). In May 2012, the Nanotechnology Knowledge Infrastructure (NKI) NSI was announced with the goal to "provide a community-based, solutions-oriented knowledge infrastructure to accelerate nanotechnology discovery and innovation" (*158*). Initial progress has been made across the IM research continuum; it is anticipated that research advances will accelerate as the NKI NSI matures.

IM-1: Develop computational models of ENM structure–property–activity relationships to support the design and development of ENMs with maximum benefit and minimum risk to humans and the environment

The NEHI agencies continue to address the crucial need for a robust data infrastructure by enhancing the availability of data for ENM research and for communication of knowledge among members of various scientific communities. There are a number of federally funded databases and platforms containing information relevant to nanoEHS: the cancer Nanotechnology Laboratory portal (caNanoLab; see cananolab.nci.nih.gov/caNanoLab), Extreme Science and Engineering Discovery Environment project (XSEDE; see www.xsede.org), InterNano (part of the NSF-sponsored National Nanomanufacturing Network; see www.internano.org), nanoHUB (part of the NSF-sponsored Network for Computational Nanotechnology; see nanohub.org), Nanomaterial-Biological Interactions Knowledgebase (NBI Knowledgebase; see nbi.oregonstate.edu), Nanomaterials Registry (see www.nanomaterialregistry.org), Nanoparticle Information Library (see www.nanoparticlelibrary.net), and EPA's ToxCast™ Program (*52*). These databases and platforms assist industrial and academic researchers and occupational health professionals in organizing and sharing information; developing high-throughput screening methods; and identifying structure–design principles for engineering high-performance, environmentally benign nanomaterials. It is critical that investments be made to maintain and expand these and other broad-based informational resources; such resources are critical to regulatory agencies, other agencies, and industry. CPSC and the NIH/National Library of Medicine have launched a project to add relevant health information concerning commercial household NEPs to the existing CPSC household products database (*159*). In 2012, this effort was expanded to include information for consumers about the uses of ENMs in NEPs and the health effects of ENMs. Finally, the three U.S.-EU Communities of Research (CORs) with an informatics focus—Databases and Ontologies, Predictive Modeling for Human Health, and Ecotoxicity Testing and Predictive Models—have been examining opportunities for common database structures, interoperability, and shared model development since their formation in 2012 (*160*).

An overarching digital data infrastructure requires the successful integration of robust digital data, including validated experimental and modeling information. The NEHI participating agencies support research to advance knowledge of ENM structural models for risk assessment, as well as resources for improved code development and validation. For example, NEHI agencies are funding research to identify general principles that determine transport and transformations of ENMs in the environment and the effects of these two processes on organisms and ecosystems (*158*). Such information is essential for predictive environmental toxicology risk assessment. Examples of predictive modeling efforts are presented in the other core research area sections of this document.

The presence of a diverse collaborative community enhances and accelerates progress in nanoinformatics through validation of shared data and codes and through advancement in the state of the science. NEHI participating agencies are funding the development of educational and training tools for improved risk assessment. For example, these efforts would allow for facile information sharing to expedite and validate the use of nanotechnology in biomedicine or for the establishment of platforms for sharing simulations, information on leading-edge instrumentation, and design, synthesis, fabrication, characterization, and integration capabilities in nanotechnology.

Implementation and Coordination of the 2011 NNI EHS Research Strategy

Coordination of the 2011 NNI EHS Research Strategy across the NEHI agencies and the six core research areas ensures integrated development and implementation of agency research programs. The NEHI Working Group, through joint alignment of research activities, has continued to actively and adaptively manage the 2011 NNI EHS Research Strategy. Highlights of its activities are provided here; additional information is available in the 2015 NNI Supplement to the President's Budget (*2*).

- *Increasing agency participation in NNI EHS research*. The 2011 NNI EHS Research Strategy identifies research areas that agencies may recognize as aligning with their missions. The number of NNI agencies participating in the implementation of the 2011 NNI EHS Research Strategy has stabilized and EHS research investments have been sustained at approximately $110 million per year, reflecting their continued high priority for the NNI. Cumulative EHS investments from 2005 through 2015 have now reached over $900 million (*2*).
- *Utilizing the NNI Coordinator for EHS Research.* An NNI Coordinator for EHS Research, first named in 2010, has facilitated efforts of the National Nanotechnology Coordination Office (NNCO), the NSET Subcommittee, and the NEHI Working Group to leverage and implement the 2011 NNI EHS Research Strategy. For example, the NNI Coordinator for EHS Research initiated an informal effort within NEHI to track and plan nanotechnology EHS research programs on a continuing basis and has represented the NNI internationally to address EHS issues about ENMs and to promote international collaborations in the field.
- *Refocusing the NEHI Working Group.* Through consultation with agency representatives, NEHI leadership continues to adapt its meetings and discussions to optimize coordination and assessment of research to achieve the goals of the 2011 NNI EHS Research Strategy. These periodic interactions allow agencies to address important research needs as they arise and to continue to improve interagency communication. This adaptive management approach facilitates the assessment of the state of science and current research, as well as the development of joint projects and programs. Examples of these efforts are found throughout this EHS research progress review.
- *Implementing media and networking opportunities.* The NSET Subcommittee and NEHI Working Group have explored social media opportunities to improve interagency communication and stakeholder interactions. NEHI held an interactive webinar in October 2011 (*161*) to introduce to stakeholders the 2011 NNI EHS Research Strategy, a substantial revision of the 2008 NNI EHS Research Strategy. Two hundred and forty participants joined the call. NNCO utilizes Twitter, Linked-in, StumbleUpon, and YouTube to communicate new EHS information. In September 2013, the NNI hosted a stakeholder workshop (*137*) that focused on linkages between risk assessment, risk management, and risk communication to better understand the types of nanotechnology EHS risk information that stakeholders are interested in, and how to convey such information to stakeholders.

- *Enabling a broad base of nanotechnology EHS research to support regulatory decision making.* The 2011 NNI EHS Research Strategy sustains a broad spectrum of basic and applied research that provides the data and information necessary for evidence-based regulatory decision making. The NEHI Working Group, meeting regularly, continues to provide a venue for research and regulatory agencies to share research developments and programs. The heightened emphasis in the 2011 NNI EHS Research Strategy on life cycle assessment provides a bridge between basic research and regulatory decision making. The NNI Coordinator for EHS Research and the NEHI Working Group have developed opportunities to integrate EHS approaches into other components of the NNI. For example, several NEHI agencies led the development in 2012 of the NKI NSI, which incorporates health and environmental impacts into data and model development. Another example of cross-component integration is the NSI announced in 2012 on Nanotechnology for Sensors and Sensors for Nanotechnology: Improving and Protecting Health, Safety, and the Environment, which includes development of sensors to measure releases of ENMs into air, water, and soil.
- *Coordinating NEHI activities with the Emerging Technologies Interagency Policy Coordination Committee (ETIPC) Working Group on Nanotechnology.* To enable information exchange among agencies on issues relating to regulatory aspects of emerging technologies, OMB's Office of Information and Regulatory Affairs (OMB/OIRA), OSTP, and the Office of the U.S. Trade Representative (USTR) established ETIPC. This committee helps ensure that Federal Government policies relating to emerging technologies—including nanotechnology—strike a proper balance between facilitating beneficial innovation and commercialization, on the one hand, and protecting human health and the environment, on the other hand. ETIPC is key to enabling responsible development of emerging technologies, including nanotechnology. ETIPC's Working Group on Nanotechnology facilitates communication among Federal agencies on many aspects of nanotechnology including regulatory developments, international information exchanges, and standards development. ETIPC has developed a set of principles specifically for regulation and oversight of emerging technologies based on the best scientific evidence (*162*, *163*). Interactions between key members of the NEHI Working Group and the ETIPC Working Group on Nanotechnology provide an important venue for regulatory discussions, particularly those with international implications.
- *Facilitating partnerships with industry.* The NEHI Working Group will continue to utilize existing Federal Small Business Innovation Research (SBIR)/Small Business Technology Transfer Research (STTR) programs and to explore and develop new mechanisms for the many different types of partnerships that NEHI agencies have with industry. Examples cited earlier are the NIOSH partnership with industries to provide guidance on process-related exposures and worker protection and the NanoRelease projects. These projects provide an opportunity for industry, not-for-profit organizations, and Federal Government representatives to work together on methods to detect, quantify, and characterize the release of ENMs in NEPs (*48*, *62*).
- *Coordinating research efforts internationally.* Multiple international research programs have been noted above in this document; four examples are: (a) the Joint Research Program: Environmental Behavior, Bioavailability and Effects of Manufactured Nanomaterials, co-funded by the U.S. EPA National Center for Environmental Research and the UK Environmental

Nanoscience Initiative (*26*); (b) the Global Exposure Measurement Harmonization effort co-led by NIOSH; (c) a formal partnership between CEINT and the International Consortium for the Environmental Implications of Nanotechnology (iCEINT) (*164*); and (d) recent outreach to China by CPSC (*165*). Several NEHI agencies also continue to participate in the OECD Working Party on Manufactured Nanomaterials (WPMN) (*78*) as it moves from the ENM EHS data collection phase into the data analysis phase. The WPMN program is designed to develop internationally accepted nanotechnology EHS testing protocols and harmonized regulatory approaches. NEHI agencies likewise participate in the OECD Working Party on Nanotechnology (WPN) (*166*), which has published several reports (*167–169*) with relevance to responsible development of nanotechnology. In 2010, the U.S. and European Commission initiated an ongoing *U.S.–EU: Bridging NanoEHS Research* dialogue, which provides an interactive platform for U.S. and EU scientists to share information on nanoEHS research interests and data needs (*160*) and to collaboratively advance the field. There have been three *U.S.–EU: Bridging NanoEHS Research Efforts* workshops (*170–172*) and there are currently six CORs focused on specific research areas of mutual interest.

- *Supporting the development of international standards.* The NEHI agencies have contributed to the substantial progress that has been made through coordinated international efforts to develop consensus standards pertaining to physico-chemical property measurements, biological property and EHS assays, nomenclature, and terminology for ENMs. The principal efforts are within two formal standards development organizations, ISO/TC 229 on Nanotechnologies and ASTM E56 on Nanotechnology. Other international organizations such as the OECD WPMN and the VAMAS Technical Working Group on Nanoparticle Populations (*173*) have contributed significantly to international consensus standards development efforts by conducting interlaboratory studies and identifying priority materials and desired testing end-points. As of April 1, 2014, more than 50 consensus standards have been released supporting the areas referenced above.
- *Adaptively managing the NNI EHS Research Strategy.* The NEHI Working Group continues to periodically review the status of nanoEHS science, progress towards achieving the goals of the 2011 NNI EHS Research Strategy, and stakeholder concerns. This document provides examples of ongoing, completed, and anticipated EHS research relevant to implementation of the 2011 NNI EHS Research Strategy.

Concluding Remarks

The NEHI Working Group generated this NNI EHS progress review to document examples of nanoEHS research activities, accomplishments, and collaborations of the NEHI member agencies for the period FY 2009 to FY 2012, as aligned with the six core research areas in the 2011 NNI EHS Research Strategy. As demonstrated by the many examples given in this review, significant research advances have been made in all of the research needs in these six core areas. A large number of these example research activities were conducted in collaboration or coordination with at least one other agency. This review also addresses progress in the implementation and coordination of the 2011 NNI EHS Research Strategy and illustrates strong stakeholder and international coordination and cooperation, notably in the development of consensus standards. Some of the many benefits of this review, both realized and anticipated, are:

- Enhanced communication of research activities among the NEHI Working Group's member agencies.
- Identification of synergistic ongoing and planned activities as well as potential research gaps that can lead to new interagency collaborations and leveraging of existing agency resources.
- Informed guidance to the NEHI participating agencies in the formulation of their own intramural and extramural research portfolios and allocation of their resources, in the context of their agency-specific missions.
- Integrated development of potential new interagency initiatives or thrust areas that can provide opportunities for enhancing and optimizing agency investments.
- Communication with myriad stakeholders about agency research accomplishments and priorities and about agency implementation and coordination of the 2011 NNI EHS Research Strategy.
- Identification of opportunities for stakeholders to participate in or leverage ongoing or planned research of the NEHI agencies.

Nanotechnology is increasingly found in many commercial and health care applications, with new NEPs developed and marketed daily. It is of paramount importance that the Federal Government provides the tools and information required to assess and manage potential risks of current and anticipated NEPs and ENMs throughout their life cycles. This goal can only be accomplished by adaptive management of the 2011 NNI EHS Research Strategy to address evolving research needs; sustained and enhanced interagency collaboration and coordination; strong international coordination of research activities and consensus standards efforts; and expanded partnerships with industry. The insight and expertise of the entire stakeholder community (including, for example, representatives from industry, academic researchers, and the public) will be critical to establishing a broad EHS knowledge base in support of regulatory decision making and responsible development of nanotechnology. The NEHI agencies are committed to realizing the vision of the 2011 NNI EHS Research Strategy—*a future in which responsible development of nanotechnology provides maximum benefit to the environment and to human social and economic well-being*.

Appendix A: Components of the 2011 NNI EHS Research Strategy

The following table lists key and subordinate research needs in the six core EHS research areas identified in the 2011 NNI EHS Research Strategy document.

Key Research Needs in the Six Core nanoEHS Research Areas

NANOMATERIAL MEASUREMENT INFRASTRUCTURE
NMI-1. **Develop measurement tools for determination of physico-chemical properties of ENMs in relevant media and during the life cycles of ENMs and NEPs** • Physical dimensions and morphology: size, size distribution, characteristic dimensions, shape • Internal structure: atomic-molecular, core-shell • Surface and interfacial properties: surface charge, zeta potential, surface structure, elemental composition, surface-bound molecular coatings and conjugates, reactivity • Bulk composition: elemental or molecular composition, crystalline phase(s) • Dispersion properties: degree and state of dispersion • Mobility and other transport properties: diffusivity, transport in biological and environmental matrices
NMI-2. **Develop measurement tools for detection and monitoring of ENMs in realistic exposure media and conditions during the life cycles of ENMs and NEPs** • Sampling and collection of ENMs • Detecting the presence of ENMs • Quantity of ENMs—concentration based on surface area, mass, and number concentrations • Size and size distribution of ENMs • Spatial distribution of ENMs • Discriminating ENMs from ambient NMs such as combustion products and welding fumes • Discriminating multiple types of ENMs such as metals and metal oxides
NMI-3. **Develop measurement tools for evaluation of transformations of ENMs in relevant media and during the life cycles of ENMs and NEPs** • Agglomeration and de-agglomeration • Dissolution and solubility • Adsorption of natural organic matter and bioconstituents • Oxidation and reduction • Deposition of ENMs on surfaces

NMI-4. Develop measurement tools for evaluation of biological responses to ENMs and NEPs in relevant media and during the life cycles of ENMs and NEPs

- Adequacy of existing assays
- New assays or high-throughput, high content assays
- Correlation of biological responses with physico-chemical properties
- Surface reactivity at the interface between ENM and biological receptors
- Biomarkers of toxicological response

NMI-5. Develop measurement tools for evaluation of release mechanisms of ENMs from NEPs in relevant media and during the life cycles of NEPs

- Release by fire, combustion, and incineration
- Release by mechanical degradation, such as abrasion, deformation, and impact
- Release by dissolution of matrix material
- Release by chemical reactions of the matrix material
- Release by photo-induced degradation of the matrix material
- Release by consumer interactions, such as spraying, mouthing, and swallowing
- Release by interactions with biological organisms in the environment

HUMAN EXPOSURE ASSESSMENT

HEA-1. Understand processes and factors that determine exposures to nanomaterials

- Conduct studies to understand processes and factors that determine exposure to engineered nanomaterials
- Develop exposure classifications of nanomaterials and processes
- Develop internationally harmonized and validated protocols for exposure surveys, sample collection and analysis, and reporting through existing and newly created international frameworks
- Develop comprehensive predictive models for exposures to a broad range of engineered nanomaterials and processes
- Characterize process- and task-specific exposure scenarios in the workplace

HEA-2. Identify population groups exposed to engineered nanomaterials

- Systematically collect and analyze information about nanomaterial manufacture, processing, and direct use in commercial and consumer products over time to discern geographic areas where engineered nanomaterials may be emitted into the environment, consumed in the form of ingredients of products, and/or disposed of in solid waste, wastewater, etc.
- Conduct population-based surveys to obtain information on use patterns for consumer products
- Identify potential subpopulations that are more susceptible to exposure to engineered nanomaterials than others
- Develop quantitative assessment methods appropriate for target population groups and conduct assessments of those population groups most likely to be exposed to engineered nanomaterials

HEA-3. Characterize individual exposures to nanomaterials • Expand currently available exposure assessment techniques to facilitate more accurate exposure assessment for engineered nanomaterials at benchmark concentration levels using feasible methods • Develop new tools through national and international surveys to support effective exposure characterization of individuals • Characterize and detect nanomaterials in biological matrices and conduct studies to understand transformations of nanomaterials during transport in the environment and in human bodies • Conduct studies to examine emissions and human contact during normal use and after wear and tear have degraded a product, as well as during repeated exposures • Develop engineered nanomaterials exposure assessment models based on identified critical exposure • Develop databases to contain the collected data and information
HEA-4. Conduct health surveillance of exposed populations • Establish a program for the epidemiological investigation of physician case reports and reports of suspicious patterns of adverse events • Establish exposure registry and medical surveillance programs for workers • Analyze injury and illness reporting in existing programs
HUMAN HEALTH
HH-1. Identify or develop appropriate, reliable, and reproducible *in vitro* and *in vivo* assays and models to predict *in vivo* human responses to ENMs • Establish a system to develop and apply reliable and reproducible *in vitro* and *in vivo* test methods • Evaluate the degree to which an *in vitro* response correlates with an *in vivo* response • Evaluate the degree to which *in vitro* and *in vivo* models predict human response • Translate structure–activity relationship and other research data into computational models to predict toxicity *in silico*
HH-2. Quantify and characterize ENMs in exposure matrices and biological matrices • Determine critical ENM measurands in biological and environmental matrices and ensure the development of tools to measure ENMs in appropriate matrices as needed • Determine matrix and/or weathering effects which may alter the physico-chemical characteristics of the ENM measurands • Identify key factors that may influence the detection of each measurand in a particular matrix (e.g., sample preparation, detection method, storage, temperature, solvents/solutions) • Characterize and quantify exposure for all exposure routes using *in vivo* models to identify the most likely routes of human exposure • Identify biomarkers of exposure and analytical methods for their determination

HH-3. Understand the relationship between the physico-chemical properties of ENMs and their transport, distribution, metabolism, excretion, and body burden in the human body

- Characterize ENM physico-chemical properties and link to mechanisms of transport and distribution in the human body
- Understand the relationship of the physico-chemical properties of ENMs to the mechanisms of sequestration in and translocation of ENMs out of the exposure organ and secondary organs, and to routes of excretion from the human body
- Determine the metabolism or biological transformation of ENMs in the human body

HH-4. Understand the relationship between the physico-chemical properties of ENMs and uptake through the human port-of-entry tissues

- Characterize ENMs at and in port-of-entry tissues, including nontraditional routes of entry such as the ear and eye, and identify mechanisms of ENM uptake into tissues
- Determine the relationship of ENM physico-chemical properties to deposition and uptake under acute exposure conditions and under chronic exposure conditions
- Translate data on ENM properties and uptake to knowledge that may be used to intentionally redesign ENMs for optimum human and environmental safety and product efficacy

HH-5. Determine the modes of action underlying the human biological response to ENMs at the molecular, cellular, tissue, organ, and whole body levels

- Determine the response and time course of biological responses at the primary site of exposure and at distal organs following ENM exposure
- Understand the mechanisms and molecular pathway(s) associated with ENM biology within cellular, organ, and whole organism systems
- Link mechanisms of response with ENM physico-chemical properties and employ this information in the design and development of future ENMs
- Develop translational alternative *in vitro* testing methods for the rapid screening of future ENMs based on mechanism(s) of response that are predictive of *in vivo* biological responses

HH-6. Determine the extent to which life stage and/or susceptibility factors modulate health effects associated with exposure to ENMs and nanotechnology-enabled products and applications

- Determine the effect of life stage and/or gender on biological response to ENMs
- Establish the role of genetic and epigenetic susceptibility on the biological response to ENMs in the context of life stage and/or susceptibility factors
- Understand mechanistically the influence of preexisting disease on the biological response to ENMs in the context of life stage and other susceptibility factors
- Identify exposure conditions that make susceptible individuals more vulnerable to the health effects associated with ENMs and nanotechnology-enabled applications
- Establish a database that contains published, peer-reviewed literature, occupational and consumer reports, and toxicological profiles that describe altered responses to ENMs and nanotechnology-enabled applications in susceptible animal models or individuals following exposure

ENVIRONMENT
ENV-1. Understand environmental exposures through the identification of principal sources of exposure and exposure routes • Manufacturing processes and product incorporation • Life cycle of technology and exposures subsequent to product manufacturing • Analytical approaches to measure temporal changes in nanoparticle properties throughout the life cycle • Models to estimate releases • Environmental receptors for exposure assessment
ENV-2. Determine factors affecting the environmental transport of nanomaterials • Determine key physico-chemical properties affecting transport • Determine key transport and fate processes relevant to environmental media • Develop new tools and adaptation of current predictive tools to accommodate unique properties of nanomaterials
ENV-3. Understand the transformation of nanomaterials under different environmental conditions • Identify and evaluate nanomaterial properties and transformation processes that will reduce environmental persistence, toxicity, and production of toxic products • Determine the rate of aggregation and long-term stability of agglomeration/aggregation and the long-term stability of these aggregates and agglomerates • Develop tools to predict the transformations or degradability of nanomaterials
ENV-4. Understand the effects of engineered nanomaterials on individuals of a species and the applicability of testing schemes to measure effects • Test protocols • Dose–response characterization • Uptake/elimination kinetics, tissue/organ distribution • Mode/mechanism of action, predictive tools • Tiered testing schemes/environmental realism
ENV-5. Evaluate the effects of engineered nanomaterials at the population, community, and ecosystem levels • Population • Community • Other ecosystem-level effects • Predictive tools for population-, community-, and ecosystem-level effects

RISK ASSESSMENT AND RISK MANAGEMENT METHODS
RAMM-1. Incorporate relevant risk characterization information, hazard identification, exposure science, and risk modeling and methods into the safety evaluation of nanomaterials • Characterization, fate, and release of nanoparticles throughout the life cycles of nanotechnology-enabled products • Development of predictive models on accumulation, migration, and release of nanoparticles throughout the life cycles of nanotechnology-enabled products • Safety of nanoparticles throughout the life cycles of the nanotechnology-enabled products • Comprehensive and predictive models to assess the potential risks of nanoparticles during the manufacturing and life cycle of nanoproducts, with inputs from human and environment exposures and material properties
RAMM-2. Understand, characterize, and control workplace exposures to nanomaterials • Dissemination and implementation of effective techniques and protocols to measure exposures in the workplace • Identification and demonstration of effective containment and control technologies including for accidents and spills • Development of an effective industry surveillance system • Design and deployment of a prospective epidemiological framework relevant to exposure science • Systematic approaches for occupational risk modeling
RAMM-3. Integrate life cycle considerations into risk assessment • Establishment of nanotechnology-specific taxonomy for life cycle stages • Integration of risk assessment, life cycle analyses, and decision-making approaches into regulatory decision making processes • Application of adaptive management tools based on monitoring/implementation to evaluate life cycle analysis implementation • Development of case studies, e.g., green chemistry, nanomaterials selection, nanomaterials acquisition process, illustrating application of these risk management methods
RAMM-4. Integrate risk assessment into decision-making frameworks for risk management • Development of comparative risk assessment and formal decision-analytical methods operating across multiple metrics as opposed to "absolute" risk assessment strategies • Application of formal decision-analytical methods (e.g., multi-criteria decision analysis) to prioritize risk management alternatives • Use of gap analyses and value of information analysis to identify research needs • Integration of stakeholder values and risk perceptions into risk management processes • Application of integrated decision framework through case studies in risk management decision making

RAMM-5. Integrate and standardize risk communication within the risk management framework • Development and use of standardized terminology in risk communications • Early information-sharing on hazards and risk among Federal agencies • Development of appropriate risk communication approaches for agency-specific needs
INFORMATICS AND MODELING (Note that in the 2011 NNI EHS Research Strategy, only one research needs category was identified.)
IM-1. Develop computational models of ENM structure–property–activity relationships to support the design and development of ENM with maximum benefit and minimum risk to humans and the environment • Validate the predictive capability of *in vitro* and *in vivo* assays and employ that subset of assays in data generation to establish computational models to predict ENM behavior in humans and the environment • Establish a standard set of physical and chemical characterization parameters, dose metrics, and biological response metrics • Design and establish structures and ontologies for methods development, data capture, sharing, and analysis • Evaluate and adapt as necessary existing computational models by beginning with existing models for exposure and dosimetry and using data generated from validated assays • Use ENM exposure and dosimetry models to develop ENM structure-activity models to predict ENM behavior in humans and the environment • Establish training sets and beta test sites to refine and validate ENM structure–activity models • Disseminate ENM structure-activity models through publicly accessible nanotechnology websites

Appendix B: Acronyms and Abbreviations

ADME	absorption, distribution, metabolism, and excretion
AFRL	Air Force Research Laboratory
ASTM E56	ASTM International's Technical Committee E56 on Nanotechnology
CEA	Comprehensive Environmental Assessment
CEIN	Center for Environmental Implications of Nanotechnology (NSF, EPA) headquartered at the University of California, Los Angeles
CEINT	Center for Environmental Implications of NanoTechnology (NSF, EPA) headquartered at Duke University
CNF	carbon nanofiber
CNT	carbon nanotube
COR	community of research
CPSC	Consumer Product Safety Commission
DHHS	Department of Health and Human Services
DOC	Department of Commerce
DOD	Department of Defense
DOE	Department of Energy
DOI	Department of the Interior
DOL	Department of Labor
EHS	environment(al), health, and safety
ELSI	ethical, legal, and societal implications (of nanotechnology)
ENM	engineered nanomaterial
ENV	Environment core research area
EPA	Environmental Protection Agency
ERDC	Engineer Research and Development Center (U.S. Army Corps of Engineers)
EU	European Union
FDA	Food and Drug Administration (DHHS)
FY	fiscal year
HEA	Human Exposure Assessment core research area
HH	Human Health core research area
IM	Informatics and Modeling core research area
ISO	International Organization for Standardization
ISO/TC 229	ISO's Technical Committee 229 on Nanotechnologies
MWCNT	multiwalled carbon nanotube
nanoEHS	nanotechnology-related environment(al), health, and safety
NCI	National Cancer Institute (DHHS/NIH)

NCL	Nanotechnology Characterization Laboratory (DHHS/NIH/NCI)
NCNHIR	NIEHS Centers for Nanotechnology Health Implications Research (Consortium)
NCTR	National Center for Toxicological Research (FDA)
NEHI	Nanotechnology Environmental and Health Implications Working Group (NSET)
NEP	nanotechnology-enabled product
NIEHS	National Institute of Environmental Health Sciences (DHHS/NIH)
NIFA	National Institute of Food and Agriculture (USDA)
NIH	National Institutes of Health (DHHS)
NIOSH	National Institute for Occupational Safety and Health (DHHS/CDC)
NISE Net	Nanoscale Informal Science Education Network (NSF)
NIST	National Institute of Standards and Technology (DOC)
NKI	Nanotechnology Knowledge Infrastructure (NSI)
NMI	Nanomaterial Measurement Infrastructure core research area
NNCO	National Nanotechnology Coordination Office
NNI	National Nanotechnology Initiative
NOM	natural organic matter
NP	nanoparticle
NRC	National Research Council of the National Academies
NSE	nanoscale science and engineering
NSET	Nanoscale Science, Engineering, and Technology Subcommittee of the NSTC Committee on Technology
NSF	National Science Foundation
NSI	Nanotechnology Signature Initiative
NSTC	National Science and Technology Council
NTP	National Toxicology Program (NIH/NIEHS)
NTRC	Nanotechnology Research Center (DHHS/NIOSH)
OECD	Organisation for Economic Co-operation and Development
OSHA	Occupational Safety and Health Administration (DOL)
RAMM	Risk Assessment and Risk Management Methods core research area
RN	research need
TiO_2	titanium dioxide
TNO	a Dutch nonprofit organization for applied scientific research
ToxCast™	toxicity forecasting research program of the National Center for Computational Toxicology (EPA)
UK	United Kingdom
USDA	U.S. Department of Agriculture
USGS	U.S. Geological Survey (DOI)

Appendix C: Research Centers and Networks

The following examples of research centers and networks are supported by several NEHI member agencies and provide opportunities and support for EHS research among investigators from a variety of disciplines and from different research sectors, including academia, industry, and government laboratories.

U.S. Government-Sponsored Collaborative nanoEHS Research Centers and Networks

CENTER	SCOPE AND DESCRIPTION	COLLABORATORS
Center for Biological and Environmental Nanotechnology (CBEN)	CBEN at Rice University fosters the development of nanotechnology through an integrated set of programs that aim to address scientific, technological, environmental, human resource, and commercialization issues. This is an NSF Nanoscale Science and Engineering Center established in 2001. The center's research program is organized under three themes: (a) wet nanoscience integrating biology and nanochemistry; (b) nanomaterials in bioengineering; and (c) environmental applications, origin, and impacts of nanostructured materials. The center works in collaboration with industry and government laboratories in developing bench-top and pilot-scale proof-of-concept testbeds. The center fosters nanoscience and engineering education by implementing course modules for upper-level undergraduates and creating an interactive webpage. CBEN's industrial affiliate program enables member companies to send their senior scientists to the center for research residency and tutorial coursework. The center also offers a year-long graduate course on entrepreneurship in nanotechnology taught by an expert team.	Baylor College DuPont EPA FDA Georgia Institute of Technology Lockheed Martin Michigan State University NIEHS North Carolina State University Purdue University University of Houston University of Texas, Austin University of Virginia
Center for Environmental Implications of Nanotechnology (CEIN)	Created in 2008 as a Nanoscale Science and Engineering Center with funding from NSF and EPA, CEIN, headquartered at UCLA, conducts predictive toxicological science for engineered nanomaterials (ENMs). It unites a highly integrated, multidisciplinary, synergistic team with the skill set to solve the complexities of environmental science, eco-toxicity, materials science, nanotechnology, biological mechanisms of injury, and the environmental fate and transport of ENMs. The center aims to develop a broad-based model of predictive toxicology premised on quantitative structure–activity relationships (QSARs) and ENM injury paradigms at the biological level. This predictive scientific model will consider (i) the ENMs most likely to come into contact with the environment; (ii) their distribution in the environment; (iii) representative environmental life forms serving as early sentinels to monitor the spread and bioaccumulation of hazardous ENMs; (iv) biological screening assays allowing QSARs to be developed based on the bio-physico-chemical properties of ENMs; (v) high-throughput screening of a combinatorial ENM	Columbia University Lawrence Berkeley National Laboratory Lawrence Livermore National Laboratory Nanyang Technological University (Singapore) Sandia National Laboratory University of Bremen (Germany) University of California (UC) Davis UC Los Angeles UC Riverside UC Santa Barbara

CENTER	SCOPE AND DESCRIPTION	COLLABORATORS
	library; and (vi) a self-learning computational system providing a framework for predictive risk analysis. These research activities are combined with educational programs informing the public, future generations of scientists, public agencies, and industrial stakeholders of the importance of safe implementation of nanotechnology in the environment. The overall impact will be to reduce uncertainty about the possible consequences of ENMs in the environment, while at the same time providing guidelines for their safe design to prevent environmental hazards. For more information, see www.cein.ucla.edu/new.	University College Dublin (Ireland) Universitat Rovira i Virgili (Spain) University of Texas at El Paso
Center for the Environmental Implications of NanoTechnology (CEINT)	CEINT, headquartered at Duke University, is dedicated to elucidating relationships between a vast array of nanomaterials—from natural to manufactured and those produced incidentally by human activities—and their potential environmental exposure, biological effects, and ecological consequences. Created in 2008 as a Nanoscale Science and Engineering Center with funding from NSF and EPA, CEINT performs fundamental research on the behavior of nanoscale materials in ecosystems that will provide guidance in assessing existing and future concerns surrounding the environmental implications of nanomaterials. For more information, see www.ceint.duke.edu.	Carnegie Mellon University Clemson University Duke University Howard University North Carolina State University Purdue University Rice University Stanford University University of Kentucky Virginia Tech
The Center for Nanoscale Science and Technology (CNST)	The CNST was established at NIST in 2007 as a unique national facility purposely designed to accelerate innovation in nanotechnology-based commerce. Its mission is to operate a national, shared resource for nanoscale fabrication and measurement and to develop innovative nanoscale measurement and fabrication capabilities in support of researchers from industry, academia, NIST, and other government agencies in advancing nanoscale technology from discovery to production. The center disseminates new nanoscale measurement methods by incorporating them into facility operations, collaborating and partnering with others, and providing international leadership in nanotechnology. For more information, see www.nist.gov/cnst.	Johns Hopkins University University of Maryland
EPA's Office of Research and Development (EPA-ORD) program on Chemical Safety for Sustainability (CSS)	The EPA-ORD program on CSS maintains a coordinated research program on the public health and environmental implications of emerging chemicals including engineered nanomaterials. The program includes extramural funding through grants and cooperative agreements, including two centers co-funded by EPA and NSF: CEIN and CEINT. The intramural program includes research in three EPA National Laboratories and two national centers, which is conducted at eight locations around the country. CSS research collaborates with OECD to generate protocols, data and risk assessment approaches to promote the safe development, use, and disposal/recycling of nanomaterials. Primary research goals are to define procedures for characterization of the physical and chemical properties of nanomaterials as manufactured and following interactions with environmental media through their life cycle; link the physical	CEIN CEINT CPSC NIEHS NSF OECD SIINN

CENTER	SCOPE AND DESCRIPTION	COLLABORATORS
	and chemical properties of nanomaterials to potential releases along the product life cycle; understand and model nanomaterial fate, transport and transformation in the environment; and identify potential adverse effects to humans and sensitive environmental species. Key research objectives include the development of validated and qualified toxicity testing methods with known predictive potential for adverse effects on human health and the environment, the provision of informational tools to inform nanomaterial risk assessments, and the generation of safer nanomaterials by informing their design and use. For more information, see epa.gov/research/docs/css-strap.pdf.	
NIEHS Engineered Nanomaterials Grand Opportunity (Nano GO) Consortium	The NIEHS Nano GO consortium supports large-scale research projects that accelerate critical breakthroughs, early and applied research on cutting-edge technologies, and new approaches to improve the synergy and interactions among multi- and interdisciplinary research teams. The major goals of this program are to develop reliable and reproducible assays, methods, and models to predict exposure and biological response to nanomaterials across different systems and laboratories. The coordinated research efforts include diverse routes of exposure to nanomaterials and *in vitro* and *in vivo* models of exposure and response. For more information, see ehp.niehs.nih.gov/1306866.	California Nanosystems Institute at UCLA East Carolina University Indiana University School of Medicine Michigan State University NIOSH New Jersey Institute of Technology North Carolina State University Pacific Northwest National Laboratory UC Berkeley UC Davis University of Montana University of Rochester University of Southern California University of Washington West Virginia University
Nanotechnology Characterization Laboratory (NCL)	The NCI established the NCL at its Frederick facility to provide critical infrastructure support to this rapidly developing field. Working in concert with NIST and FDA, NCL is accelerating the transition of basic nanotechnology-biotechnology research into clinical applications. NCL specifically aims to establish and standardize an analytical cascade for nanomaterial characterization; facilitate the clinical development and regulatory review of nanomaterials for cancer clinical trials; identify and characterize critical parameters related to nanomaterials' ADME and toxicity profiles of nanomaterials using animal models; examine the biological and functional characteristics of multicomponent/combinatorial aspects of nanoscaled therapeutic, molecular and clinical diagnostics, and detection platforms; engage and facilitate academic- and industrial-based knowledge sharing of nanomaterial performance data and behavior resulting from preclinical testing; and interface with other nanotechnology efforts.	ASTM International FDA The Foundation for Advanced Education in the Sciences Institute for Food Technologists NIST

CENTER	SCOPE AND DESCRIPTION	COLLABORATORS
The Network for Computational Nanotechnology (NCN)	NCN was established in 2002 by NSF and has grown to be a national resource serving the research community in the emerging field of nanoscience and nanotechnology. NCN is producing new knowledge, simulation approaches, numerical algorithms, and open-source software to help realize the promise of nanoscience. NCN researchers are carrying out simulation and modeling research in three key fundamental research themes: nanoelectronics, nanoelectromechanical systems/nanofluidics, and nanobiology and medicine. The vision of NCN is to provide a future in which a diverse community, united by a common culture and enabled by a shared cyber-infrastructure, uses theory, modeling, and simulation to accelerate the transformation of nanoscience to nanotechnology. The NCN goals and objectives are to (a) carry out research that addresses key challenges through theory, modeling, and simulation; (b) provide professional leadership that brings communities together to identify challenges and move the field ahead; (c) develop new software tools needed for this new field; (d) lower barriers that limit the use of simulation by experimentalists and educators and equip them to be critical, effective users; (e) develop and deploy cyber-infrastructure that efficiently and robustly delivers services for simulation, education, and collaboration; (f) educate and develop a workforce to increase the number and diversity of students and faculty engaged in nanotechnology; (g) disseminate the results of NCN's work; and (h) engage the broader community through universally available web technology. For more information, see nanohub.org/groups/ncn.	Columbia University The Multimedia Educational Resource for Learning and Online Teaching (MERLOT) Norfolk State University Northwestern University Purdue University Stanford University UC Berkeley University of Florida at Gainesville University of Illinois at Urbana-Champaign University of Texas at El Paso
NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR) Consortium	The NCNHIR Consortium is an interdisciplinary program consisting of five U19 and three U01 Cooperative Centers along with other active grantees funded through NIEHS's nanoEHS program. NIEHS also established contractual agreements for nanomaterial characterization and an informational database to support this consortium. The overarching goals of these efforts are to gain fundamental understanding on how the physical and chemical properties of ENMs influence the interactions of ENMs with biological systems and to better understand potential health risks associated with ENM exposure. These findings will also guide safe development and use of nanotechnology.	Indiana University New Jersey Institute of Technology New York University Oregon State University Pacific Northwest National Laboratory RTI International UC Davis UC Los Angeles University of Michigan University of Montana University of Southern California University of Washington

CENTER	SCOPE AND DESCRIPTION	COLLABORATORS
National Center for Toxicological Research (NCTR)	NCTR is the only FDA center located outside the Washington DC metropolitan area. The one-million square foot research campus in Jefferson, Arkansas, plays a critical role in the missions of FDA and DHHS to promote and protect public health. Regulatory science researchers, academics, and other regulatory science research organizations and groups from around the world investigate, learn, and train at the Federal facility.	NIEHS NTP Wright-Patterson Air Force Base
Nanotechnology Research Center (NTRC)	The NIOSH Nanotechnology Research Center (NTRC) was established in 2004 to develop, coordinate, and deliver an organized research program that identifies, investigates, and develops science-based solutions to workplace health and safety knowledge gaps in nanotechnology. NTRC provides overall strategic direction and coordination of the NIOSH nanotechnology cross-sector research program. NTRC is spread out over several NIOSH laboratories (Cincinnati, Morgantown, and Pittsburgh). Results from these research activities are also reported in current intelligence bulletins (CIBs), which are issued to disseminate new scientific information about occupational hazards. CIBs are distributed to representatives of academia, industry, organized labor, public health agencies, and public interest groups, as well as to Federal agencies responsible for ensuring the safety and health of workers. For more information, see www.cdc.gov/niosh/topics/nanotech.	Applied Research Associates College of Nanoscale Science and Engineering, University at Albany, State University of New York CPSC DOD The Hamner Institutes for Health Sciences Research Institute of Occupational Medicine Lovelace Respiratory Research Institute NIEHS NIST NSF NTP Partnership for European Research in Occupational Safety and Health OECD OSHA TNO
The Nanoscale Informal Science Education Network (NISE Net)	Originally launched in 2005 with support from the NSF, NISE Net is a national community of researchers and informal science educators dedicated to fostering public awareness, engagement, and understanding of nanoscale science, engineering, and technology. NISE Net aims to engage the public in advances in nanoscale research, capture the imagination of young people who may subsequently choose careers in nanoscale science and engineering (NSE), and foster new partnerships among research institutions and informal science centers. NISE Net partners have created a nation-wide set of annual events called NanoDays; developed dozens of interactive exhibits, media-based products, programs, and public forums based on NSE; generated new knowledge about the design for learning about NSE, its applications, and societal implications; produced a network that involves informal educators and researchers; and developed a website for professionals, www.nisenet.org, that includes several resources for educators and researchers, including a catalog of	Association of Science-Technology Centers Center for Nanotechnology in Society at Arizona State University Children's Museum of Houston Exploratorium The Franklin Institute Lawrence Hall of Science Museum of Life and Science Museum of Science Boston New York Hall of Science Oregon Museum of Science and Industry

CENTER	SCOPE AND DESCRIPTION	COLLABORATORS
	educational products. NISE Net will continue to develop new educational products, deepen the involvement of current partnerships in nanoscale informal science education, and expand the number of partners overall to 300 organizations. The advisory committee, content steering committee, regional hubs, and other work groups develop collaborative relationships between museums and university-based NSE research centers, including Materials Research Science and Engineering Research Centers (MRSECs) and Nanoscale Science and Engineering Centers (NSECs). A Diversity, Equity, and Access group actively supports, fosters, and encourages NISE Net's efforts to reach diverse audiences with regard to geography, disability, gender, race/ethnicity, language, and income. Four types of research studies are being conducted: Partnership and Network, Institutional Change, Learning Progressions, and Evidence-Based Decision Making.	Sciencenter Materials Research Society Science Museum of Minnesota SRI International

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